Form PTO-1390 (REV 11-2000)	US DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER
		4856-CIP
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		US APPLICATION NO (If known, see 37 CFR 15) 09/914501
INTERNATIONAL APPLICATION NO. PCT/US00/05364	INTERNATIONAL FILING DATE 01 March 2000	PRIORITY DATE CLAIMED 01 March 1999

TITLE OF INVENTION
METHOD OF DIAGNOSING AND MONITORING MALIGNANT BREAST CARCINOMAS

APPLICANT(S) FOR DO/EO/US
STRECKFUS, CHARLES F.; BIGLER, LENORA G.; THIGPEN, JAMES TATE

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ The U.S. has been elected by the expiration of the 19th month from the priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the international Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Articles 19 or 34 (35 U.S.C. 371(c)(3))
   a. ☒ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ have been transmitted by the International Bureau in English.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report Under PCT Article 36 (35 U.S.C. 371(c)5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items of information: Copy of Small Entity Statement for Priority Application and Assertion of Small Entity Status

US APPLICATION NO (if known, see 37 CFR 1.5) 09/914501	INTERNATIONAL APPLICATION NO. PCT/US00/05364	ATTORNEY'S DOCKET NUMBER 4856-CIP

21. ☒ The following fees are submitted: **BASIC NATIONAL FEE (37 CFR 1.492(a) (1) – (5)):**		CALCULATIONS PTO USE ONLY	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO.	**$1000.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO.	**$860.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	**$710.00**		
☒ International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(I)-(4).	**$690.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(I)-(4).	**$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =		$690	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	20-20 =	0	X **$18.00**	$	
Independent claims	3 -3 =	0	X **$80.00**	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+**$270.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$690	
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).				$345	
SUBTOTAL =				$345	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$345	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$345	
				Amount to be Refunded:	$
				Charged:	$

a. ☒ A check in the amount of $345 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 18-0882. **A duplicate copy of this sheet is enclosed.**

d. ☐ Fees are to be charged to a credit card. **WARNING**: Information on this form may become public. **Credit card information should not be included on this form.** Provice credit card information and authorization on PTO-2038.

Note: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

CUSTOMER No. 22922

Reinhart, Boerner, Van Deuren,
Norris & Rieselbach, s.c.
Attn: Linda Gabriel, Docket Clerk
1000 North Water Street, Suite 2100
Milwaukee, WI 53202-0900
414-298-8360

SIGNATURE: Rodney DeKruif

Rodney D. DeKruif
NAME

35,853
REGISTRATION NUMBER

MW\766982

CERTIFICATION UNDER 37 CFR 1.10 MAILING

I hereby certify that, on the date shown below, the following documents are being deposited with the United States Postal Service in an envelope addressed to BOX PCT, Assistant Commissioner for Patents, Washington, D.C. 20231 via Express Mail No. EL835272099US on August 29, 2001:

- ☒ Transmittal Letter to the United States Designated/Elected Office (DO/EO/US) Concerning a Filing Under 35 U.S.C. 371 (with a duplicate copy of Page 2 for deposit account)
- ☒ Letter Under Rule 66.8
- ☒ Statement Under Article 34(2)(b)
- ☒ Response to Written Opinion
- ☒ Preliminary Amendment
- ☒ Marked up Version Showing Changes to First Page of Patent Application
- ☒ Verified Statement of Small Entity
- ☒ Assertion of Small Entity Status
- ☒ Check No. 0067161 in the amount of $345.00

Rodney D. DeKruif

Date: August 29, 2001

Attorney Docket No. 4856-CIP

PATENT

I hereby certify that this paper or fee is being deposited with the United States Postal Service as Express Mail No. EL732810692US in an envelope addressed to: International Preliminary Examining Authority, ATTN: PCT US/RO, Commissioner for Patents, Washington, DC 20231 on April 6, 2001.

Reinhart, Boerner, Van Deuren,
Norris & Rieselbach, s.c.

Dated: April 6, 2001

BY: Rodney D. DeKruif

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :
University of Mississippi Medical Center)

Serial No: PCT/US00/05364)

Filed: 01 March 2000)

For: METHOD OF DIAGNOSING AND MONITORING MALIGNANT BREAST CARCINOMAS) Attorney Docket No. : 4856-PCT

International Preliminary Examining Authority
Commissioner for Patents
Washington, DC 20231

LETTER UNDER RULE 66.8

Dear Sir:

Attached hereto are replacement sheets to account for amendments to several claims, under Article 34(2)(b).

The claims now submitted differ from those originally filed only with respect to claims 1, 10 and 15. The claims are amended to clarify the invention and better distinguish it over the prior art cited in the Written Opinion. The accompanying Response (to the Written Opinion) briefly discusses the prior art, supports the amendments and patentably distinguishes the subject invention over the prior art.

Claims 1, 10 and 15, as originally filed, are hereby amended and provided on replacement sheets 28, 29 and 30, respectively.

If any questions remain as to the claim amendments or the replacement sheets submitted in support thereof, an invitation is hereby extended to contact the undersigned by telephone.

Respectfully submitted,

BY Rodney D. DeKruif
Attorney for Applicant

Reinhart, Boerner, Van Deuren,
Norris & Rieselbach, s.c.
1000 North Water Street, Ste. 2100
Milwaukee, WI 53202-3186
414-298-8360

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :
University of Mississippi Medical Center

Serial No: PCT/US00/05364

Filed: 01 March 2000

For: METHOD OF DIAGNOSING AND MONITORING MALIGNANT BREAST CARCINOMAS

Attorney Docket No. : 4856-PCT

International Preliminary Examining Authority
Commissioner for Patents
Washington, DC 20231

RESPONSE TO WRITTEN OPINION

Dear Sir:

The Authority issued a Reasoned Statement under Rule 66.2 with regard to novelty, inventive step and industrial applicability, providing therewith comments and explanations in support thereof. The Authority's statement is well-taken; however, in light of the present submission, the Authority is encouraged to reconsider its position and prepare an International Preliminary Examination Report entirely favorable to Applicants.

Even though novelty was indicated in the affirmative with respect to several claims, the remaining claims were cited as lacking novelty, and all claims were indicated as lacking inventive step. The Streckfus abstract was cited as the basis for this indication for the reasons provided in the opinion. Applicants respectfully disagree with the

Authority and patentably distinguish the claimed invention over Streckfus, as provided below.

With respect to one aspect of this invention, Applicants' position begins with the understanding that whole saliva is a mixture including salivary gland secretion and cellular components. (See, Mandel, "Sialochemistry", pp. 321-325 and Table 3.) Serum proteins are not expected to be found in fluid secretions from the salivary glands; i.e., saliva fluid or salivary secretion. (See, Baum, "Age Changes in Salivary Glands and Salivary Secretion", p. 115.) The electrolyte (including protein) concentration of saliva fluid secretion is markedly different from plasma (serum) because it reflects an active transport system and is relatively independent of serum concentration. Saliva secretion protein levels are a mere fraction of the corresponding serum levels. (See, Mandel, *supra*.)

In light of this background information, consider the presence of epidermal growth factor (EGF) in the salivary secretion component of whole saliva. EGF has a molecular weight comparable to the erb biomarker claimed as part of the present invention. (See, Dobrosielski-Vergona, "The Biology of the Salivary Glands", pp. 370-371.) The size and molecular weight of EGF dictate that its presence in salivary secretion is by some mechanism other than passive diffusion from serum into the glandular cells, then from those cells as part of salivary secretion. Rather, it is known that EGF is synthesized in the cells of the saliva gland and present in the salivary secretion by way of an active transport system. (See, Cook, et al., "Secretion by the Major Salivary Glands", pp. 1093-1094.)

As a point of comparison, consider the presence of various other proteins in whole saliva. In contrast to EGF, such constituents are much smaller in dimension and of

significantly lower molecular weight. Even if such constituents diffuse passively from serum, it has been observed that they are not found in the salivary secretion. Rather, histochemical staining shows their presence restricted to the cellular component of whole saliva. (See, Cook, *supra*.) The Mandel, Baum, Dobrosielski-Vergona, and Cook references can be provided upon request. Alternatively, the Authority is referred to the pending U.S. priority application for copies filed in support thereof.

Accordingly, there would be no expectation in the art as a whole to find the erb and related protein biomarkers of this invention in the salivary secretion component of whole saliva. Quite the opposite, the presence of such biomarkers would be expected, in light of the art, to be limited to the cellular component of whole saliva, just as are proteins of much lower molecular weight.

Independent claims 1, 10 and 15 are amended herewith to clarify the present invention and more appropriately distinguish it over the prior art. In particular, the claimed invention is patentably distinguished over the Streckfus abstract. Streckfus neither discloses nor suggests the presence of the referenced biomarkers as part of and/or soluble in the salivary secretion component of whole saliva, and Streckfus does not describe using such secretion in conjunction with the invention claimed. Rather, Streckfus is representative of the prior art, disclosing only the presence of tissue biomarkers in whole saliva. But for the present invention, the art would restrict the presence of the claimed biomarkers to the cellular component of whole saliva. The detection of such constituents in salivary secretion and use thereof as part of a diagnostic method is patentably distinguishable over the prior art, including the Streckfus abstract.

Support for the present amendments (to claims 1, 10 and 15 on replacement sheets 28, 29 and 30, respectively) is found throughout the specification of the application, in particular, in light of Examples 8a and 8e. The biomarkers of this invention were found to be secreted by one or more salivary glands. Their concentration in this fluid component of whole saliva was found to lack contribution from the cellular component. Such biomarkers can be constituents in a reference panel against which the salivary secretion concentration of an individual biomarker is compared. No new matter is added.

In light of the present response, the Authority is encouraged to reconsider its opinion. Applicants' respectfully request preparation of an International Preliminary Examination Report confirming, in the affirmative, novelty, inventive step and industrial applicability of the present invention.

Respectfully submitted,

BY 

Rodney D. DeKruif
Attorney for Applicants
Registration No. 35,853

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PATENT

I hereby certify that this paper or fee is being deposited with the U.S. Postal Service as Express Mail No. EL835272099US in an envelope addressed to: Box PCT, Assistant Commissioner for Patents, Washington, D.C. 20231, August 29, 2001.

Dated: August 29, 2001

Reinhart, Boerner, Van Deuren, Norris & Rieselbach, s.c.

BY: Rodney D. DeKruif

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of : Streckfus, et al.	)	
	)	Group Art Unit:
International Application No. PCT/US00/05364	)	
	)	
Serial No.:	)	
	)	Attorney Docket: 4856-CIP
International Filing Date: March 1, 2000	)	
	)	
For: Method of Diagnosing and Monitoring Malignant Breast Carcinomas	)	

Assistant Commissioner for Patents
Washington, D.C. 20231

ASSERTION OF SMALL ENTITY STATUS

Sir:

The undersigned, having determined applicant is entitled to small entity status, hereby claims such status for purposes pertaining to the present application and makes payment of an exact small entity basic filing fee, pursuant to 37 CFR §§ 1.27 and 1.492.

Please contact the undersigned by telephone if any issue remains.

Respectfully submitted,

BY Rodney D. DeKruif
Attorney for Applicant
Registration No. 35,853

Reinhart, Boerner, Van Deuren,
Norris & Rieselbach, s.c.
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